REMARKS

Upon entry of this amendment, claims 1-36 are pending. Claims 37-39 have been canceled without prejudice or disclaimer as drawn to a non-elected invention. Claims 1, 5, 8, 14, 15, 18, 21, 24 and 27 have been amended. Support for the amendments to these claims can be found in the originally filed claims, and in the specification at, *e.g.*, page 9, lines 15-17[ml]. No new matter is added.

Claim Rejections -- 35 U.S.C. § 112, second paragraph

Claims 1-36 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Examiner states that claims 1, 18 and 24 are unclear because the representation results of the generated output signals "are set forth as limitations (i) and (ii) in said step (b) as being directed to (i), a length between target occurrences, and (ii), identities of various target subsequences," and in step (c) "each such representation is compared to 'different nucleotide sequences' of a second population." However, step (b) does not generate sequence(s) per se. (Office action, page 2).

Applicants have amended claims 1, 18 and 24 to more precisely claim the subject matter of the invention. Particularly, claims 1, 18, and 24 have been amended herein to recite that the output signals are a representation of (i) the distance between occurrences of target nucleotide subsequences in the first nucleic acid, and (ii) the identities of the target nucleotide subsequences or sets of target nucleotide subsequences in the first nucleic acid. Also, the phrase "the different nucleotide sequences of" in step (d) (formerly step (c)) has been deleted from claims 1, 18 and 24. These claims now recite in step (d) that each representation provided by the first sample is compared with the second population by generating a statistical score. As such, Applicants submit that claims 1, 18, and 24 (as well as dependent claims 2-18, 19-23, and 35-36), as amended herein, are clear and definite. Therefore, this rejection should be withdrawn.

The Examiner has also indicated that claims 1, 8, 18, 21, 24 and 27 are unclear as the term "different" lacks proper antecedent basis in step (a) (now step (b)) when there is only one recognition means is used for probing. (Office action, page 3).

Applicants have amended claims 1, 8, 18, 21, 24 and 27 to provide new step (b) (formerly step (a)), which recites "probing said first sample with one or more recognition means, each

recognition means recognizing a target nucleotide subsequence or a set of target nucleotide subsequences, wherein if said first sample is probed with two or more recognition means, each recognition means recognizes a different target nucleotide subsequence or a different set of target nucleotide subsequences." As amended, these claims require a different target nucleotide subsequence or a different set of target nucleotide subsequences only if the first sample is probed with two or more recognition means. Thus, Applicants respectfully submit that there is proper antecedent basis for the term "different" in amended claims 1, 8, 18, 21, 24 and 27 (and claims depending thereon), and respectfully request that this rejection be withdrawn.

Claim Rejections -- 35 U.S.C. § 102(b)

Claims 1-3, 5, 8-10, 15, 18-29, 31 and 35 are rejected under 35 U.S.C. § 102(b) as being anticipated over Helentjaris *et al.*, United States Patent number 5,385,835 ("Helentjaris"). Applicants traverse this rejection to the extent that it applies to the claims as presently amended.

The Examiner states that Helentjaris is "directed to the generation of RFLPs which represent the length between loci of nucleic acids separated by said RFLPs," and "teaches the three steps of the above-listed claims." (Office action at pages 3-4). The Examiner indicates that various Figures in Helentjaris provide that "statistical correlation values depict the representation of signals which show RFLPs as well as identities of RLFP target regions," and that "[r]ecognition means for probing sample nucleic acid populations are described via cloned probes and/or Southern blotting." (Office action at pages 3-4). Additionally, the Examiner states that the last step of claim 1 is disclosed by the genotype population correlations, allegedly taught by Helentjaris at column 9, lines 19-55. (*Id.*). Applicants respectfully disagree.

Helentjaris is directed to methods of determining the relationship between restriction fragment length polymorphisms ("RFLPs") and one or more quantitative traits in plants. (See, Helentjaris, col. 6, lines 4-8; and claim 1). Helentjaris teaches that the RFLP probes can be randomly chosen or can be selected from an RFLP genetic linkage map. (See, Helentjaris, col. 6, lines 23-28). Applicants respectfully submit that Helentjaris does not anticipate the claims as amended herein because Helentjaris does not teach each limitation of the pending claims.

First, the pending claims require the generation, from a sample containing a population of nucleic acids, one or more output signals that are a representation of both the distance between occurrences of target nucleotide subsequences in the first nucleic acid, and the identities of the

target nucleotide subsequences or sets of target nucleotide subsequences in the first nucleic acid. The RFLP analysis as taught by Helentjaris, however, does not generate an output signal that represents the distance between occurrences of target nucleotide subsequences in a nucleic acid. Specifically, Helentjaris teaches that, when genomic DNAs from two genetically distinct individuals are digested with a restriction enzyme, electrophoresed and probed with a labeled DNA clone, polymorphisms in the hybridization pattern result due to sequence differences termed "restriction fragment length polymorphisms." (Helentjaris at col 2, lines 40-47). Helentjaris also teaches that agarose gel electrophoresis can be used to show differences in fragment lengths between the two genetically distinct individuals. (*Id.* at col 2, lines 48-50). However, Helentjaris does not teach any output signal representing the length of a restriction fragment or the distance between occurrences of a target nucleotide subsequences in a nucleic acid.

Second, the pending claims require that the output signal generated from the nucleic acid(s) of the first sample indicates the presence or absence of the nucleic acid(s) in the second sample. While Helentjaris teaches that sequence differences between individuals may result in polymorphisms in the hybridization pattern (presumably due to the presence or absence in a restriction enzyme site on a nucleic acid), Helentjaris does not teach that the presence or absence of the nucleic acid itself can be determined from the generated output signals.

Third, with respect to independent claims 1, 18, and 24, and their respective dependent claims, Helentjaris does not teach that the nucleic acid sequences of the second population are known. As amended herein, independent claims 1, 18, and 24, and their respective dependent claims, require two populations of nucleic acids: a first population of first nucleic acids having different nucleotide sequences, and second population of second nucleic acids having different nucleotide sequences, where the different nucleotide sequences of the second population are known. In the claimed methods, knowledge of the nucleotide sequences of the second population is useful in determining the sequence of the nucleic acids present in the first population, since the determination that nucleic acids of known sequence are present in both the first and second populations provides the sequence information for the nucleic acid in the first population, thereby overcoming the requirement of sequencing the nucleic acid of the first population.

Finally, independent claim 27, and its respective dependent claims, requires that the one or more output signals generated at step (b) includes "a representation of (i) the distance between occurrences of target nucleotide subsequences in said first nucleic acid, (ii) the identities of said target nucleotide subsequences in said first nucleic acid or the identities of said sets of target nucleotide subsequences among which are included the target nucleotide subsequences in said first nucleic acid, and (iii) a measure of the level/amount of the first nucleic acid in the first sample producing the output signal." (Emphasis added). In contrast, Helentjaris teaches the presence or absence of a specific restriction enzyme site in a nucleic acid, which can be used to determine the association of an RFLP with a given phenotype, but Helentjaris does not teach that the RFLPs can be used to determine the level or amount of the first nucleic acid in the first sample, as required by amended claim 27 and its dependent claims. Therefore, Helentjaris does not teach every limitation of these claims.

Thus, Helentjaris does not teach or suggest all the limitations of claims 1-3, 5, 8-10, 15, 18-29, 31 and 35, as amended herein, and the rejection under 35 U.S.C. § 102 (b) should be withdrawn.

CONCLUSION

Based on the instant amendments and remarks, Applicants submit that this application is in condition for allowance and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact Applicants' undersigned attorney at the telephone number indicated below.

Respectfully submitted,

Dated: July 29, 2004

Ivor R. Elrifi, Reg. No. 39,529, Reg. No. 45,899
Attorney for Applicant
MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY and POPEO, P.C.
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No. 30623

TRA 1943799v1